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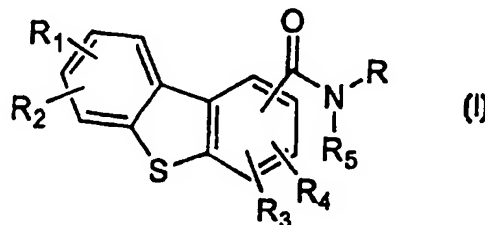
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(54) Title: N-AMINOALKYLDIBENZOTHIOPHENECARBOXAMIDES; DOPAMINE RECEPTOR SUBTYPE SPECIFIC LIGANDS

(57) Abstract

Disclosed are compounds of formula (I) or the pharmaceutically acceptable acid addition salts thereof, wherein R₁, R₂, R₃, R₄ are the same or different and represent hydrogen, C₁-C₆ alkyl, halogen, hydroxy, amino, cyano, nitro, trifluoromethyl, trifluoromethoxy, C₁-C₆ alkoxy, -O₂CR', -NHCOR', -COR', -SO_mR', where R' is C₁-C₆ alkyl and wherein m is 0, 1 or 2; or R₁, R₂, R₃, R₄ independently represent -CONR''R'' or -NR''R'' where R' and R'' independently represent hydrogen or C₁-C₆ alkyl; R₅ is hydrogen or C₁-C₆ alkyl; and R represents an aminoalkyl group, which compounds

are useful in the treatment of affective disorders such as schizophrenia, depression, Alzheimer's disease, movement disorders such as Parkinsonism and dystonia, and other disorders which respond to dopaminergic blockade such as substance abuse and obsessive compulsive disorders. Further, compounds of this invention may be useful in treating the extrapyramidal side effects associated with the use of conventional neuroleptic agents.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
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**N-AMINOALKYLDIBENZOTHIOPHENECARBOXAMIDES: DOPAMINE RECEPTOR SUBTYPE
SPECIFIC LIGANDS**

5

BACKGROUND OF THE INVENTION**Field of the invention**

This invention relates to dibenzothiophenecarboxamide derivatives which selectively bind to brain dopamine receptor subtypes. More specifically, it relates to N-aminoalkyldibenzothiophenecarboxamides and to pharmaceutical compositions comprising
10 such compounds. It further relates to the use of such compounds in the treatment or prevention of various neuropsychological disorders such as schizophrenia and other central nervous system diseases.

Description of the Related Art

15 The therapeutic effect of conventional antipsychotics, known as neuroleptics, is generally believed to be exerted through blockade of dopamine receptors. However, neuroleptics are frequently responsible for undesirable extrapyramidal side effects (EPS) and tardive dyskinesias, which are attributed to blockade of D₂ receptors in the striatal region of the brain. The dopamine D₃ receptor subtype has recently been identified (Sokoloff et al.,
20 Nature, 347: 146 (1990). Its unique localization in limbic brain areas and its differential recognition of various antipsychotics suggest that the D₃ receptor may play a major role in the etiology of schizophrenia. Selective D₃ antagonists may be effective antipsychotics free from the neurological side effects displayed by conventional neuroleptics. Compounds of the present invention demonstrate high affinity and selectivity in binding to the D₃ receptor
25 subtype. They may be of potential use in treatment of schizophrenia, psychotic depression and mania. Other dopamine-mediated diseases such as Parkinsonism and tardive dyskinesias may also be treated directly or indirectly by modulation of D₃ receptors.

United States Patent 5,395,835 discloses N-aminoalkyl-2-naphthalamides which have affinity at dopamine D₃ receptors. The compounds the present invention differ significantly
30 from this prior art in that they possess a dibenzothiophenecarboxamide substructure.

Murray et al., in Bioorg. Med. Chem. Let., 5: 219 (1995), describes 4-carboxamido-biphenyls said to have affinity for dopamine D₃ receptors.

SUMMARY OF THE INVENTION

This invention provides novel compounds of Formula I which interact with dopamine receptor subtypes. Thus, the invention provides compounds of general Formula I useful in the treatment and/or prevention of various neuropsychological disorders. The invention also
5 provides pharmaceutical compositions comprising compounds of Formula 1.

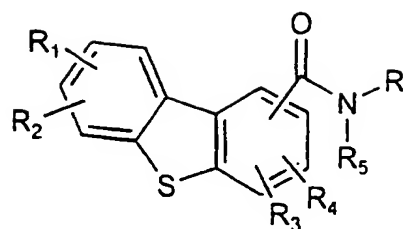
The invention further relates to the use of such compounds and compositions in the treatment of affective disorders such as schizophrenia, depression, Alzheimer's disease and certain movement disorders such as Parkinsonism and dystonia. Compounds of this invention are also useful in treating the extrapyramidal side effects associated with the use of
10 conventional neuroleptic agents. Further, the compounds of the present invention are useful for the treatment of other disorders which respond to dopaminergic blockade such as substance abuse and obsessive compulsive disorder.

Since dopamine D₃ receptors are concentrated in the limbic system (Taubes, *Science* 265 (1994) 1034) which controls cognition and emotion, compounds which interact with
15 these receptors also have utility in the treatment of cognitive disorders. Such disorders include cognitive deficits which are a significant component of the negative symptoms (social withdrawal and unresponsiveness) of schizophrenia. Other disorders involving memory impairment or attention deficit disorders can also be treated with the compounds of this invention that interact specifically with the dopamine D₃ receptor subtype.

20 Furthermore, compounds of this invention may be useful in treatment of depression, memory-impairment or Alzheimer's disease by modulation of D₃ receptors which selectively exist in limbic area known to control emotion and cognitive functions. The compounds of the present invention are also useful for the treatment of other disorders which respond to dopaminergic blockade such as substance abuse (Caine and Koob, *Science*, 260: 1814 (1993))
25 and obsessive compulsive disorder (Goodman et al., *Clin. Psychopharmacol.*, 7: 35 (1992)). The interaction of the compounds of the invention with dopamine receptor subtypes is demonstrated below. This interaction results in the pharmacological activities of these compounds.

Accordingly, a broad embodiment of the invention is directed to a compound of

Formula I:



I

or the pharmaceutically acceptable acid addition salts thereof, wherein:

- 5 R_1, R_2, R_3, R_4 are the same or different and represent hydrogen, C_1-C_6 alkyl, halogen, hydroxy, amino, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_1-C_6 alkoxy, $-O_2CR'$, $-NHCOR'$, $-COR'$, $-SO_mR'$, where R' is C_1-C_6 alkyl and wherein m is 0, 1 or 2;

or

- 10 R_1, R_2, R_3, R_4 independently represent $-CONR'R''$, or $-NR'R''$ where R' and R'' independently represent hydrogen or C_1-C_6 alkyl;

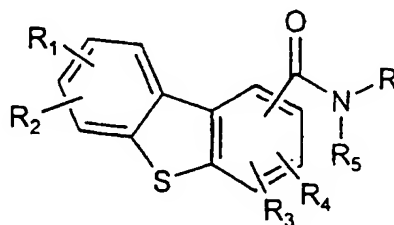
R_5 is hydrogen or C_1-C_6 alkyl; and

R represents an aminoalkyl group.

- Thus, the invention relates to the use of compounds of formula I in the treatment
 15 and/or prevention of neuropsychochological disorders including, but not limited to, schizophrenia, mania, dementia, depression, anxiety, compulsive behavior, substance abuse, memory impairment, cognitive deficits, Parkinson-like motor disorders and motion disorders related to the use of neuroleptic agents.

DETAILED DESCRIPTION OF THE INVENTION

In addition to compounds of general formula I described above, the invention encompasses compounds of general formula IA:

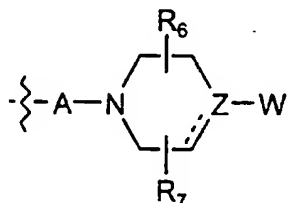


IA

wherein:

R₁, R₂, R₃, R₄, R₅ are as defined above; and

R represents an aminoalkyl group of the formula



where

A represents an alkylene group of 2 to 6 carbon atoms optionally substituted with one or more alkyl groups having from 1 to 4 carbon atoms;

Z is N or C;

R₆ and R₇ are the same or different and represent hydrogen or C₁-C₆ alkyl; or

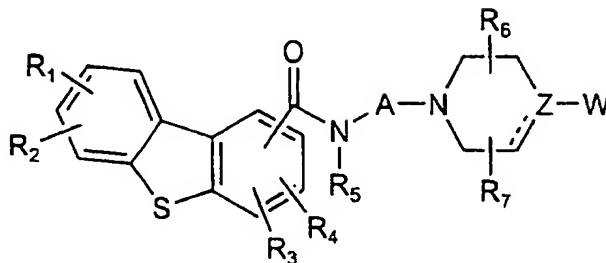
R₆ and R₇ together with the the 6-membered ring to which they are attached form a 5 to 8-membered ring; and

W is phenyl, naphthyl, 1-(5,6,7,8-tetrahydro)naphthyl or 4-(1,2-dihydro)indenyl, pyridinyl, pyrimidyl, quinoliny, isoquinoliny, benzofuranyl, benzothienyl; each of which is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₄ alkoxy, thioalkoxy, hydroxy, amino, monoalkylamino, dialkylamino, cyano, nitro, trifluoromethyl or trifluoromethoxy.

Preferred compounds of formula IA include those where R₁-R₄ are hydrogen and A is

alkylene of 3-5 carbon atoms.

In addition to compounds of general formula I described above, the invention encompasses compounds of general formula IB:



IB

wherein:

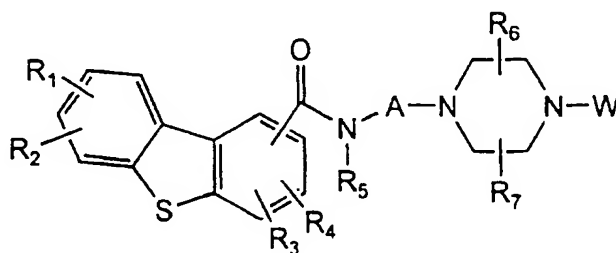
R_1 , R_2 , R_3 , R_4 , and R_5 are as defined above;

R_6 and R_7 are the same or different and represent hydrogen or C_1 - C_6 alkyl; or

10 R_6 and R_7 together with the the 6-membered ring to which they are attached form a 5 to 8-membered ring; and

A, Z and W are as defined above.

The present invention further encompasses compounds of Formula II:



II

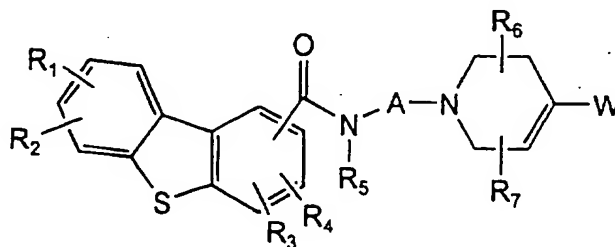
wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , and R_7 , A, and W are as defined above.

Preferred compounds of formula II are those where R_1 - R_5 are hydrogen; A is C_3 - C_5 alkylene; and W is quinolinyl, naphthyl or a phenyl group optionally substituted with up to
20 three groups independently selected from halogen, C_1 - C_6 alkyl, C_1 - C_4 alkoxy, thioalkoxy, hydroxy, amino, monoalkylamino, dialkylamino, cyano, nitro, trifluoromethyl or

trifluoromethoxy. More preferred compounds of formula II are those where R_1 - R_5 are hydrogen; A is C_3 - C_5 alkylene; and W is 8-quinolinyl, naphthyl or a phenyl group optionally substituted with up to two groups in the 2 and/or 3 positions (relative to the point of attachment of the phenyl group to the piperazine ring), the groups being independently selected from halogen, C_1 - C_4 alkyl, and C_1 - C_4 alkoxy. Particularly preferred compounds of formula II are those where R_1 - R_5 are hydrogen; A is C_4 alkylene; and W is 8-quinolinyl, naphthyl or a phenyl group optionally up to two groups in the 2 and/or 3 positions (relative to the point of attachment of the phenyl group to the piperazine ring), the groups being independently selected from chloro, methyl, and methoxy.

10

The present invention further encompasses compounds of Formula III:

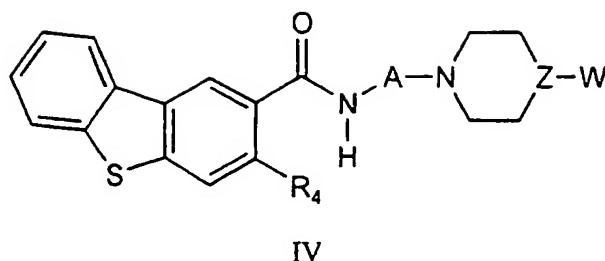


III

wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , and R_7 , A, and W are as defined above.

Preferred compounds of formula III are those where R_1 - R_5 are hydrogen; A is C_3 - C_5 alkylene, more preferably butylene; and W is quinolinyl, naphthyl or phenyl optionally substituted with up to three groups independently selected from halogen, C_1 - C_6 alkyl, C_1 - C_4 alkoxy, thioalkoxy, hydroxy, amino, monoalkylamino, dialkylamino, cyano, nitro, trifluoromethyl or trifluoromethoxy. Particularly preferred compounds of formula III are those where R_1 - R_5 are hydrogen; A is C_3 - C_5 alkylene, more preferably butylene; and W is 8-quinolinyl, naphthyl, or phenyl.

The invention also provides compounds of Formula IV



where

R₄ is hydrogen or C₁-C₄ alkoxy;

5 A represents alkylene group of 2 to 6 carbon atoms;

Z is nitrogen or carbon; and

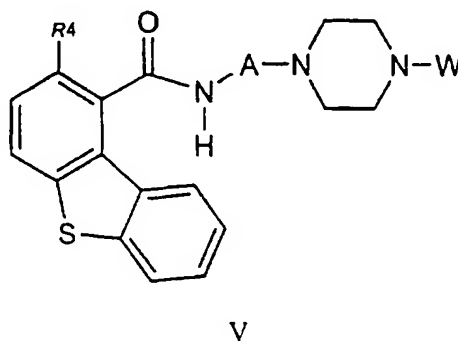
W is quinolinyl, phenyl or naphthyl, each of which is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₄ alkoxy, thioalkoxy, hydroxy, amino, monoalkylamino, dialkylamino, cyano, nitro, trifluoromethyl or trifluoromethoxy.

10

Preferred compounds of formula IV are those where R₄ is hydrogen and A is C₃-C₅ alkylene. More preferred compounds of formula IV are those where R₄ is hydrogen; A is C₄ alkylene; Z is nitrogen; and W is 8-quinolinyl, naphthyl or phenyl optionally substituted with up to two groups in the 2 and/or 3 positions (relative to the point of attachment of the phenyl group to the 6-membered nitrogen-containing ring), the groups being independently selected

15

The invention further provides compounds of Formula V



20

where

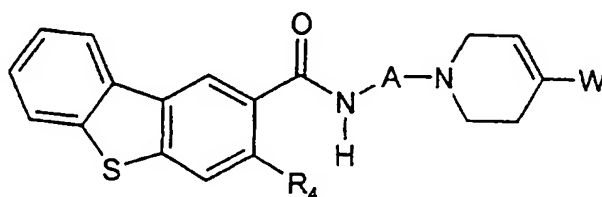
R₄ is hydrogen or C₁-C₄ alkoxy;

A represents alkylene group of 2 to 6 carbon atoms; and

W is quinolinyl, phenyl or naphthyl, each of which is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₄ alkoxy, thioalkoxy, hydroxy, amino, monoalkylamino, dialkylamino, cyano, nitro, trifluoromethyl or trifluoromethoxy.

Preferred compounds of formula V are those where R₄ is C₁-C₄ alkoxy and A is C₃-C₅ alkylene. More preferred compounds of formula V are those where R₄ is C₁-C₄ alkoxy; A is C₄ alkylene; and W is 8-quinolinyl, naphthyl or phenyl optionally substituted with up to two groups in the 2 and/or 3 positions (relative to the point of attachment of the phenyl group to the piperazine ring), the groups being independently selected from halogen, C₁-C₄ alkyl, and C₁-C₄ alkoxy. Particularly preferred compounds of formula V are those where R₄ is C₁-C₄ alkoxy; A is C₄ alkylene; and W is 8-quinolinyl, naphthyl, or a phenyl group substituted in the 2 position (relative to the point of attachment of the phenyl group to the piperazine ring) with a C₁-C₄ alkoxy, preferably methoxy, group.

The invention also provides compounds of Formula VI



VI

where

R₄ is hydrogen or C₁-C₄ alkoxy;

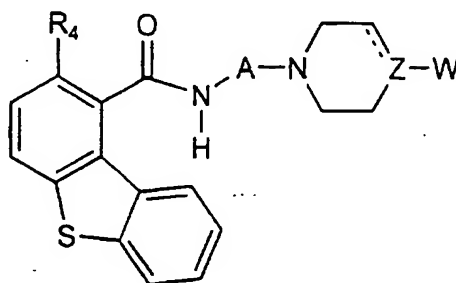
A represents alkylene group of 2 to 6 carbon atoms; and

W is quinolinyl, phenyl or naphthyl, each of which is optionally substituted with up to three groups independently selected from halogen, C₁-C₆ alkyl, C₁-C₄ alkoxy, thioalkoxy, hydroxy, amino, monoalkylamino, dialkylamino, cyano, nitro, trifluoromethyl or trifluoromethoxy.

Preferred compounds of formula VI are those where R₄ is hydrogen and A is C₃-C₅

alkylene. More preferred compounds of formula VI are those where R_4 is hydrogen; A is C_4 alkylene; and W is 8-quinolinyl, naphthyl or phenyl optionally substituted with up to two groups in the 2 and/or 3 positions (relative to the point of attachment of the phenyl group to the 6-membered nitrogen-containing ring), the groups being independently selected from
 5 halogen, C_1 - C_4 alkyl, and C_1 - C_4 alkoxy.

The invention also provides compounds of Formula VI-A



VI-A

10 where

R_4 is hydrogen or C_1 - C_4 alkoxy;

A represents alkylene group of 2 to 6 carbon atoms;

Z is nitrogen or carbon; and

W is quinolinyl, phenyl or naphthyl, each of which is optionally substituted with up to three
 15 groups independently selected from halogen, C_1 - C_6 alkyl, C_1 - C_4 alkoxy, thioalkoxy, hydroxy, amino, monoalkylamino, dialkylamino, cyano, nitro, trifluoromethyl or trifluoromethoxy.

Preferred compounds of formula VI-A are those where R_4 is hydrogen and A is C_3 - C_5 alkylene. More preferred compounds of formula VI-A are those where R_4 is hydrogen; A is
 20 C_4 alkylene; Z is nitrogen; and W is 8-quinolinyl, naphthyl or phenyl optionally substituted with up to two groups in the 2 and/or 3 positions (relative to the point of attachment of the phenyl group to the 6-membered nitrogen-containing ring), the groups being independently selected from halogen, C_1 - C_4 alkyl, and C_1 - C_4 alkoxy.

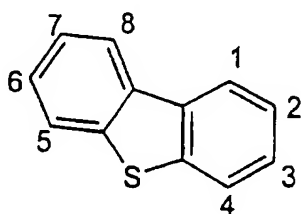
25 When a compound of the invention is obtained as a mixture of enantiomers, these

enantiomers may be separated, when desired, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, for example using a chiral HPLC column.

Representative compounds of the present invention, which are encompassed by
5 Formula I, include, but are not limited to the compounds in Figure I and their pharmaceutically acceptable salts. The present invention also encompasses prodrugs, e.g., acylated prodrugs, of the compounds of Formula I. Those skilled in the art will recognize various synthetic methodologies which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and prodrugs of the compounds encompassed by
10 Formula I.

Representative compounds of the present invention, which are encompassed by Formula I, include, but are not limited to the compounds in Table 1 and their pharmaceutically acceptable salts. Non-toxic pharmaceutically acceptable salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic,
15 toluenesulfonic, methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanolic such as acetic, $\text{HOOC}-(\text{CH}_2)_n-\text{COOH}$ where n is 0-4, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

The following numbering system is used to identify positions on the dibenzofuran ring portion of the compounds of the invention:

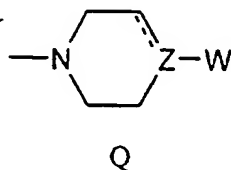


20 By "alkyl" and "lower alkyl" is meant straight and branched chain alkyl groups having from 1-6 carbon atoms, e.g., C_1 - C_6 alkyl.

By "lower alkoxy" and "alkoxy" is meant straight and branched chain alkoxy groups
25 having from 1-6 carbon atoms, e.g., C_1 - C_6 alkoxy.

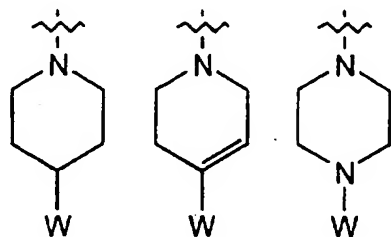
By halogen is meant fluorine, chlorine, bromine and iodine.

The amino portion of the aminoalkyl group represented by R above includes groups represented by the formula Q



5 where W is defined above.

The formula Q represents saturated heterocyclic ring systems such as, for example, piperidinyl and piperazinyl, as well as unsaturated heterocyclic ring systems such as, for example, 1, 2, 3, 6-tetrahydropyridine. Preferred Q groups are the following:

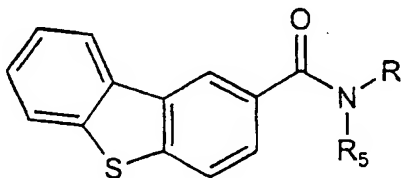


10 where W is defined above.

Particularly preferred W groups of the invention are (a) quinolinyl, more preferably 8-quinolinyl, (b) naphthyl, or (c) phenyl optionally substituted with up to two substituents independently selected from halogen, C₁-C₄ alkyl, and C₁-C₄ alkoxy. These optional phenyl substituents are preferably in the 2 and/or 3 positions of the phenyl group relative to the point of attachment of the phenyl group to the 6-membered nitrogen containing ring.

Representative examples of N-aminoalkyldibenzothiophenecarboxamides according to the invention are shown in Table 1 below. The number below each compound is its compound number. Each of these compounds may be prepared according to the general reaction Scheme I set forth below.

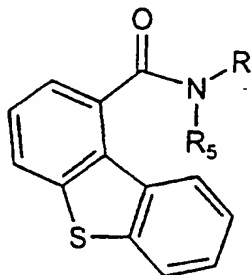
20 Compounds 1-8 in Table 1 have the following general formula A:



A

where R and R₅ are defined in the table.

Compounds 9-11 in Table 1 have the following general formula B:

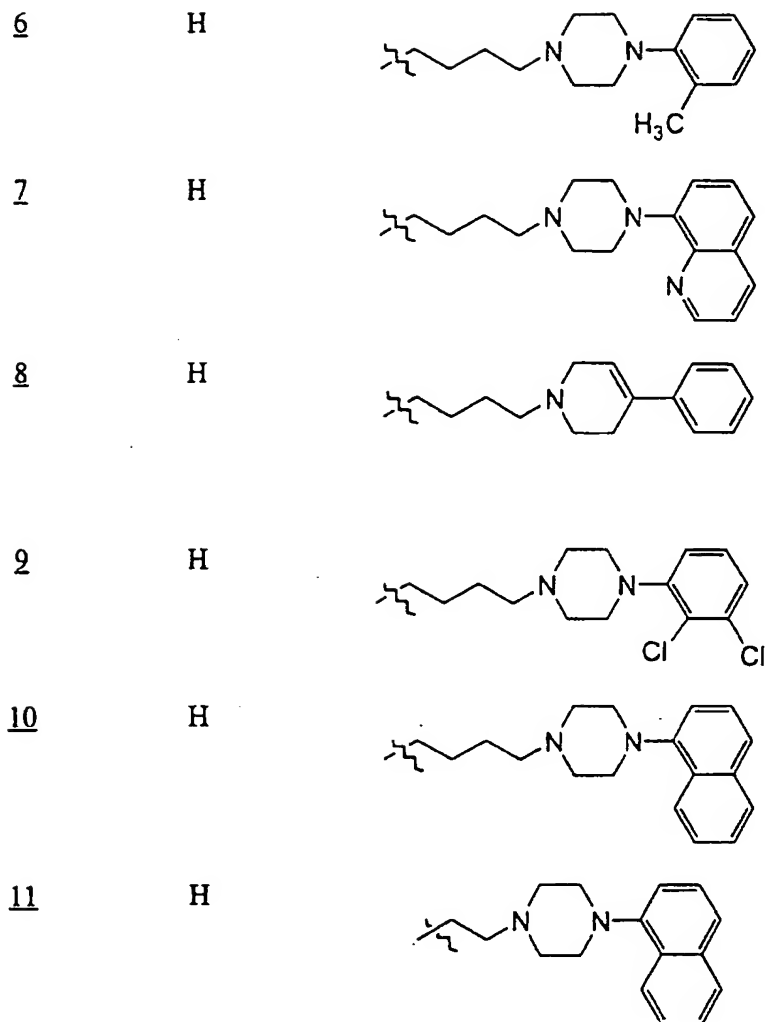


B

where R and R₅ are defined in the table.

Table 1

Compound Number	R ₅	R
<u>1</u>	H	
<u>2</u>	H	
<u>3</u>	H	
<u>4</u>	H	
<u>5</u>	H	



Particular compounds according to the invention include:

- | | |
|----|----------------------------------------------------------------------------------------------------------|
| 5 | N-(1-{4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]} butyl)-2-dibenzothiophene-carboxamide hydrochloride |
| 10 | N-(1-{4-[4-(1-Naphthyl)piperazin-1-yl]} butyl)-2-dibenzothiophenecarboxamide hydrochloride |
| 15 | N-(1-{4-[4-(2-Methyl-3-chlorophenyl)piperazin-1-yl]} butyl)-2-dibenzothiophene-carboxamide hydrochloride |
| | N-(1-{4-[4-(2,3-Dimethylphenyl)piperazin-1-yl]} butyl)-2-dibenzothiophene-carboxamide hydrochloride |
| | N-(1-{4-[4-(2-Chlorophenyl)piperazin-1-yl]} butyl)-2-dibenzothiophene-carboxamide hydrochloride |

N-(1-{4-[4-(2-Methylphenyl)piperazin-1-yl]} butyl)-2-dibenzothiophene-carboxamide hydrochloride

5 N-(1-{4-[4-(8-Quinoliny)]piperazin-1-yl]} butyl)-2-dibenzothiophenecarboxamide hydrochloride

10 N-(1-{4-[4-Phenyl-1,2,3,6-tetrahydropyridin-1-yl]} butyl)-2-dibenzothiophene-carboxamide hydrochloride

N-(1-{4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]} butyl)-1-dibenzothiophene-carboxamide hydrochloride

15 N-(1-{4-[4-(1-Naphthyl)piperazin-1-yl]} butyl)-1-dibenzothiophenecarboxamide hydrochloride

N-(1-{2-[4-(1-Naphthyl)piperazin-1-yl]} ethyl)-1-dibenzothiophenecarboxamide hydrochloride

20 The invention also pertains to the use of compounds of general Formula I in the treatment of neuropsychological disorders. The pharmaceutical utility of compounds of this invention are indicated by the following assays for dopamine receptor subtype affinity.

ASSAY FOR D₂ AND D₃ RECEPTOR BINDING ACTIVITY

25 Pellets of COS cells containing recombinantly produced D₂ or D₃ receptors from African Green monkey were used for the assays. The sample is homogenized in 100 volumes (w/vol) of 0.05 M Tris HCl buffer at 4° C and pH 7.4. The sample is then centrifuged at 30,000 x g and resuspended and rehomogenized. The sample is then centrifuged as described and the final tissue sample is frozen until use. The tissue is resuspended 1:20 (wt/vol) in 0.05
30 M Tris HCl buffer containing 100 mM NaCl.

Incubations are carried out at 48°C and contain 0.4 ml of tissue sample, 0.5 nM ³H-YM 09151-2 and the compound of interest in a total incubation of 1.0 ml. Nonspecific binding is defined as that binding found in the presence of 1 mM spiperone; without further additions, nonspecific binding is less than 20% of total binding. The binding characteristics
35 of representative compounds of the invention for D₂ and D₃ receptor subtypes are shown in Table 2 for rat striatal homogenates.

TABLE 2

Compound Number ¹	D ₃ K _i (nM)	D ₂ K _i (nM)
1	3.5	285
2	5.0	242

¹ Compound numbers relate to compounds shown above in Table 1.

The compounds of general Formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier. One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The

tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

5 Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

 Aqueous suspensions contain the active materials in admixture with excipients suitable
10 for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or
15 condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions
20 may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

 Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil
25 such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

 Dispersible powders and granules suitable for preparation of an aqueous suspension by

the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

5 Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty
10 acids and hexitol, anhydrides, for example sorbitan monoleate, and condensation products of the and partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a
15 preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or
20 solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono or diglycerides. In addition, fatty acids such as oleic acid find use in the
25 preparation of injectables.

The compounds of general Formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug.

Such materials are cocoa butter and polyethylene glycols.

Compounds of general Formula I may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives
5 and buffering agents can be dissolved in the vehicle.

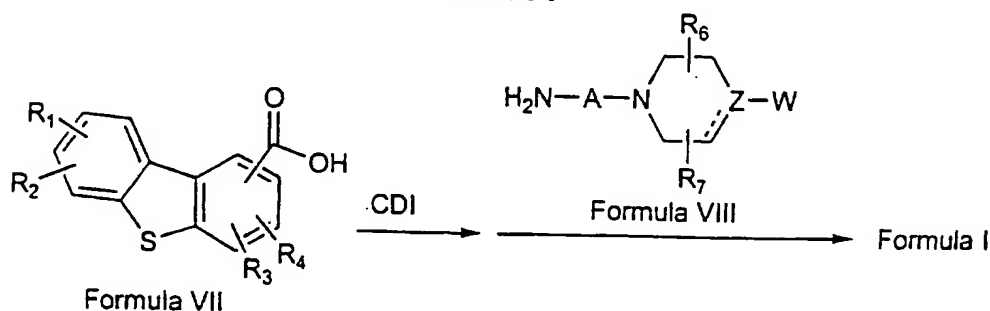
Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host
10 treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of
15 administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

Preparation of N-aminoalkyldibenzothiophenecarboxamides

The compounds of Formula I, and the pharmaceutically acceptable acid addition salts thereof, may be prepared according to the reactions shown below in Scheme 1.
20

Scheme 1



wherein R₁, R₂, R₃, R₄, R₅, R₆, R₇, A, Z and W are as defined above for Formula IA.

25 As shown, a compound of Formula VII may be activated by 1,1'-carbonyldiimidazole

(CDI) or the like in solvents such as tetrahydrofuran at room temperature. The resulting activated species may be subsequently reacted with the required compound of Formula VIII to afford a compound of Formula I as the desired product.

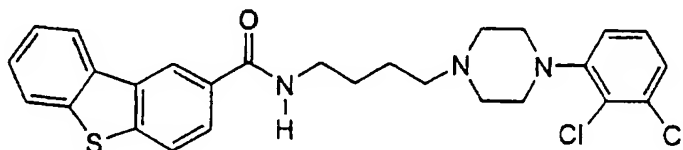
Where they are not commercially available, the compounds of Formula VII may be prepared by literature procedures or procedures analogous to those described in literature. The compounds of Formula VIII are either known or capable of being prepared by various methods known in the art.

Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention, as demonstrated by the following examples. In some cases protection of certain reactive functionalities may be necessary to achieve some of the above transformations. In general the need for such protecting groups will be apparent to those skilled in the art of organic synthesis as well as the conditions necessary to attach and remove such groups.

The disclosures in this application of all articles and references, including patents, are incorporated herein by reference.

The invention is illustrated further by the following examples which are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them. These examples illustrate the presently preferred methods for preparing the compounds of the invention.

Example 1



N-(1-{4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]}-butyl)-2-dibenzothiophenecarboxamide

2-Dibenzothiophenecarboxylic acid (105 mg, 0.45 mmol) and 1,1'-carbonyldiimidazole (80 mg, 0.5 mmol) are stirred in 20 mL tetrahydrofuran at room temperature overnight. A solution of 4-[4-(2,3-dichlorophenyl)piperazin-1-yl]-1-aminobutane

(150 mg, 0.5 mmol) in 5 mL of tetrahydrofuran is added. The resulting mixture is stirred for another 2 hours. The reaction mixture is then partitioned between dichloromethane and 10% aqueous sodium bicarbonate solution. The organic layer is dried (Na_2SO_4) and concentrated *in vacuo*. The resulting oil is subjected to preparative TLC using 10:1:0.1 dichloromethane-methanol-ammonium hydroxide as eluent. This affords the title compound as the free base. The hydrochloride salt is prepared by treating the free base with diethyl ether-HCl. The resulting hydrochloride salt of the title compound has a melting point of 238-240 °C.

Example 2

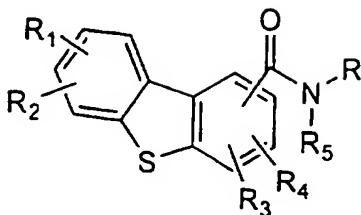
The following compounds of Formula 1 are prepared essentially according to the procedures set forth in Example 1 above.

- (a) N-(1-{4-[4-(1-Naphthyl)piperazin-1-yl]} butyl)-2-dibenzothiophenecarboxamide hydrochloride (mp 225-228 °C)
- (b) N-(1-{4-[4-(2-Methyl-3-chlorophenyl)piperazin-1-yl]} butyl)-2-dibenzothiophene-carboxamide hydrochloride (mp 230-231 °C)
- (c) N-(1-{4-[4-(2,3-Dimethylphenyl)piperazin-1-yl]} butyl)-2-dibenzothiophene-carboxamide hydrochloride (mp 226-228 °C)
- (d) N-(1-{4-[4-(2-Chlorophenyl)piperazin-1-yl]} butyl)-2-dibenzothiophene-carboxamide hydrochloride (mp 226-228 °C)
- (e) N-(1-{4-[4-(2-Methylphenyl)piperazin-1-yl]} butyl)-2-dibenzothiophene-carboxamide hydrochloride (mp 232-235 °C)
- (f) N-(1-{4-[4-(8-Quinoliny)]piperazin-1-yl]} butyl)-2-dibenzothiophenecarboxamide hydrochloride (mp 235-238 °C)
- (g) N-(1-{4-[4-Phenyl-1,2,3,6-tetrahydropyridin-1-yl]} butyl)-2-dibenzothiophene-carboxamide hydrochloride (mp 266-268 °C)
- (h) N-(1-{4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]} butyl)-1-dibenzothiophene-carboxamide hydrochloride (mp 220-222 °C)
- (i) N-(1-{4-[4-(1-Naphthyl)piperazin-1-yl]} butyl)-1-dibenzothiophenecarboxamide hydrochloride (mp 222-223 °C)
- (j) N-(1-{2-[4-(1-Naphthyl)piperazin-1-yl]} ethyl)-1-

dibenzothiophenecarboxamide hydrochloride (mp 215-218 °C)

What is claimed is:

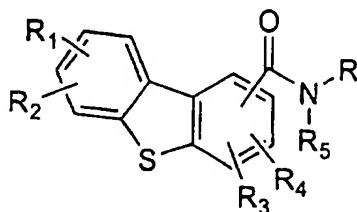
1. A compound of the formula:



or the pharmaceutically acceptable acid addition salts thereof, wherein:

- 5 R_1, R_2, R_3, R_4 are the same or different and represent hydrogen, C_1-C_6 alkyl, halogen, hydroxy, amino, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_1-C_6 alkoxy, $-O_2CR'$, $-NHCOR'$, $-COR'$, $-SO_mR'$, where R' is C_1-C_6 alkyl and wherein m is 0, 1 or 2;
or
 R_1, R_2, R_3, R_4 independently represent $-CONR'R''$, or $-NR'R''$ where R' and R'' independently
10 are hydrogen or C_1-C_6 alkyl;
 R_5 is hydrogen or C_1-C_6 alkyl; and
 R represents an aminoalkyl group.

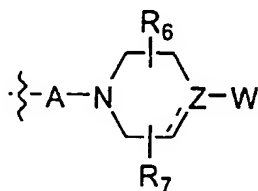
2. A compound of the formula:



wherein:

- 15 R_1, R_2, R_3, R_4 are the same or different and represent hydrogen, C_1-C_6 alkyl, halogen, hydroxy, amino, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_1-C_6 alkoxy, $-O_2CR'$, $-NHCOR'$, $-COR'$, $-SO_mR'$, where R' is C_1-C_6 alkyl and wherein m is 0, 1 or 2;
or
20 R_1, R_2, R_3, R_4 independently represent $-CONR'R''$, or $-NR'R''$ where R' and R'' independently are hydrogen or C_1-C_6 alkyl;
 R_5 is hydrogen or C_1-C_6 alkyl; and

R represents an aminoalkyl group of the formula



where

A represents an alkylene group of 2 to 6 carbon atoms optionally substituted with one
5 or more alkyl groups having from 1 to 4 carbon atoms;

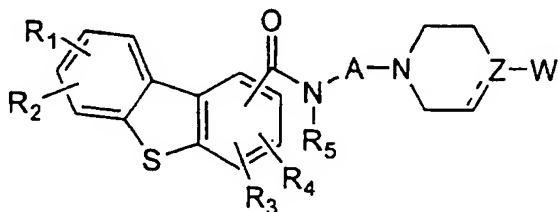
Z is N or C;

R₆ and R₇ are the same or different and represent hydrogen or C₁-C₆ alkyl; or

R₆ and R₇ together with the the 6-membered ring to which they are attached form a 5
to 8-membered ring; and

10 W is phenyl, naphthyl, 1-(5,6,7,8-tetrahydro)naphthyl or 4-(1,2-dihydro)indenyl,
pyridinyl, pyrimidyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothienyl;
each of which is optionally substituted with up to three groups independently
selected from halogen, C₁-C₆ alkyl, C₁-C₄ alkoxy, thioalkoxy, hydroxy,
amino, monoalkylamino, dialkylamino, cyano, nitro, trifluoromethyl or
15 trifluoromethoxy.

3. A compound of the formula:



wherein:

20 R₁, R₂, R₃, R₄ are the same or different and represent hydrogen, C₁-C₆ alkyl, halogen,
hydroxy, amino, cyano, nitro, trifluoromethyl, trifluoromethoxy, C₁-C₆ alkoxy, -
O₂CR', -NHCOR', -COR', -SO_mR', where R' is C₁-C₆ alkyl and wherein m is 0, 1 or 2;

or

R_1, R_2, R_3, R_4 independently represent $-\text{CONR}'\text{R}''$, or $-\text{NR}'\text{R}''$ where R' and R'' independently are hydrogen or $\text{C}_1\text{-C}_6$ alkyl;

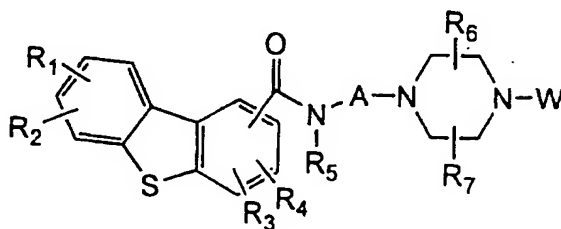
R_5 is hydrogen or $\text{C}_1\text{-C}_6$ alkyl;

A represents an alkylene group of 2 to 6 carbon atoms optionally substituted with one or more
5 alkyl groups having from 1 to 4 carbon atoms;

Z is N or C; and

W is phenyl, naphthyl, 1-(5,6,7,8-tetrahydro)naphthyl or 4-(1,2-dihydro)indenyl, pyridinyl, pyrimidyl, isoquinolinyl, quinolinyl, benzofuranyl, benzothienyl; each of which is optionally independently substituted with up to three groups selected from halogen,
10 $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_4$ alkoxy, thioalkoxy, hydroxy, amino, monoalkylamino, dialkylamino, cyano, nitro, trifluoromethyl or trifluoromethoxy.

4. A compound according to Claim 1, which is



15 wherein

R_6 and R_7 are the same or different and represent hydrogen or $\text{C}_1\text{-C}_6$ alkyl; or

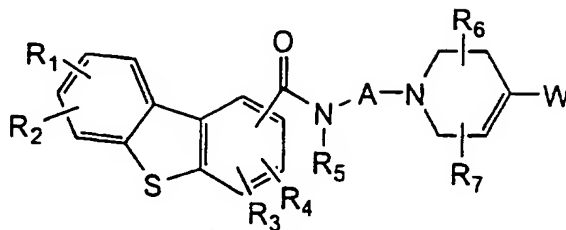
R_6 and R_7 together with the the 6-membered ring to which they are attached form a 5 to 8-membered ring; and

A represents an alkylene group of 2 to 6 carbon atoms optionally substituted with one or more
20 alkyl groups having from 1 to 4 carbon atoms;

Z is N or C; and

W is phenyl, naphthyl, 1-(5,6,7,8-tetrahydro)naphthyl or 4-(1,2-dihydro)indenyl, pyridinyl, pyrimidyl, isoquinolinyl, quinolinyl, benzofuranyl, benzothienyl; each of which is optionally independently substituted with up to three groups selected from halogen,
25 $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_4$ alkoxy, thioalkoxy, hydroxy, amino, monoalkylamino, dialkylamino, cyano, nitro, trifluoromethyl or trifluoromethoxy.

5. A compound according to claim 1 which is



5 wherein

R₆ and R₇ are the same or different and represent hydrogen or C₁-C₆ alkyl; or

R₆ and R₇ together with the the 6-membered ring to which they are attached form a 5 to 8-membered ring; and

A represents an alkylene group of 2 to 6 carbon atoms optionally substituted with one or more

10 alkyl groups having from 1 to 4 carbon atoms;

Z is N or C; and

W is phenyl, naphthyl, 1-(5,6,7,8-tetrahydro)naphthyl or 4-(1,2-dihydro)indényl, pyridinyl, pyrimidyl, isoquinolinyl, quinolinyl, benzofuranyl, benzothienyl; each of which is optionally independently substituted with up to three groups selected from halogen, C₁-C₆ alkyl, C₁-C₄ alkoxy, thioalkoxy, hydroxy, amino, monoalkylamino, 15 dialkylamino, cyano, nitro, trifluoromethyl or trifluoromethoxy.

6. A compound according to Claim 1, which is N-(1-{4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]} butyl)-2-dibenzothiophenecarboxamide hydrochloride.

20

7. A compound according to Claim 1, which is N-(1-{4-[4-(1-Naphthyl)piperazin-1-yl]} butyl)-2-dibenzothiophenecarboxamide hydrochloride

8. A compound according to Claim 1, which is N-(1-{4-[4-(2-Methyl-3-chlorophenyl)piperazin-1-yl]} butyl)-2-dibenzothiophenecarboxamide hydrochloride.

25

9. A compound according to Claim 1, which is N-(1-{4-[4-(2,3-Dimethylphenyl)piperazin-1-yl]} butyl)-2-dibenzothiophenecarboxamide hydrochloride.

10. A compound according to Claim 1, which is N-(1-{4-[4-(2-Chlorophenyl)piperazin-1-yl]} butyl)-2-dibenzothiophenecarboxamide hydrochloride.

11. A compound according to Claim 1, which is N-(1-{4-[4-(2-Methylphenyl)piperazin-1-yl]} butyl)-2-dibenzothiophenecarboxamide hydrochloride.

12. A compound according to Claim 1, which is N-(1-{4-[4-(8-Quinoliny)l)piperazin-1-yl]} butyl)-2-dibenzothiophenecarboxamide hydrochloride.

13. A compound according to Claim 1, which is N-(1-{4-[4-Phenyl-1,2,3,6-tetrahydropyridin-1-yl]} butyl)-2-dibenzothiophenecarboxamide hydrochloride.

14. A compound according to Claim 1, which is N-(1-{4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]} butyl)-1-dibenzothiophenecarboxamide hydrochloride.

15. A compound according to Claim 1, which is N-(1-{4-[4-(1-Naphthyl)piperazin-1-yl]} butyl)-1-dibenzothiophenecarboxamide hydrochloride.

16. A compound according to Claim 1, which is N-(1-{2-[4-(1-Naphthyl)piperazin-1-yl]} ethyl)-1-dibenzothiophenecarboxamide hydrochloride.

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D333/76 C07D409/12 A61K31/495 A61K31/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS, vol. 33, no. 6, 1968, PRAGUE CS, pages 1873-1879, XP002034748 K. PELZ ET AL.: "Neurotrope und psychotrope Substanzen XXIII. Über einige substituierte Dibenzothiophen-Derivate" see page 1875 - page 1876; example III see abstract	1
A	---	2-16
A	JOURNAL OF MEDICINAL CHEMISTRY, vol. 24, no. 9, 1981, WASHINGTON US, pages 1107-1110, XP002034749 C. R. ELLEFSON ET AL.: "Synthesis and Evaluation of 1,2,3,4-Tetrahydro[1]benzothieno[2,3-h]isoquinolines as Dopamine Antagonists" see the whole document ---	1-16
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

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- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
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- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *&* document member of the same patent family

Date of the actual completion of the international search

8 July 1997

Date of mailing of the international search report

1 7. 07. 97

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INTERNATIONAL SEARCH REPORT

PCT/US 97/04661

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 109 815 A (LILLY CO ELI) 30 May 1984 see abstract; claims ---	1-16
A	US 5 395 835 A (GLASE SHELLY A ET AL) 7 March 1995 cited in the application see the whole document -----	1-16

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		GB 2130209 A,B	31-05-84
		JP 59108748 A	23-06-84
		US 4500545 A	19-02-85

US 5395835 A	07-03-95	AU 1877495 A	09-10-95
		CA 2180155 A	28-09-95
		EP 0751939 A	08-01-97
		FI 963294 A	23-08-96
		HU 76058 A	30-06-97
		NO 963996 A	23-09-96
		PL 316313 A	06-01-97
		WO 9525727 A	28-09-95
		ZA 9502382 A	10-01-96
